In the specification:

Please amend the specification at page 1 as indicated in Appendix D. A clean copy of the specification at page 1 is set forth in Appendix C.

REMARKS

Claims 1-14 and 17-18 are currently pending. A clean version of the pending claims is submitted herewith as Appendix A. Claims 1, 2, 4, 6, 8-11 and 14 have been amended, and a marked-up version of the amended claims is submitted herewith as Appendix B. Applicants respectfully request reconsideration of pending claims 1-14 and 17-18.

Applicants have amended page 1 of the specification to update the status of the priority application, which is now abandoned. Applicants thank the Examiner for this suggestion. A clean copy and a marked-up copy of the amended sentence with the updated priority information are submitted herewith as Appendices C and D, respectively. No new matter has been introduced into the specification or claims by amendment.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-14 and 17-18 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner asserting that the specification does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. This ground of rejection is respectfully traversed.

The Examiner asserts that the specification as originally filed does not provide support for the recitation in claim 1 of "composition comprising at least one purified antibody specific against C5" (Office Action, paragraph 5). The Examiner's interpretation of this traditional open language is not understood, but in a sincere attempt to advance prosecution, claim 1 has been amended to delete recitation of "at least one" which appears to have confused the Examiner, and to recite "composition comprising a purified antibody specific against C5." No new matter has been added by way of this amendment, for which support is found throughout the specification, *e.g., inter alia,* at page 29, lines 14-21, and Examples 1-8, pages 37-60.

Applicants submit that claim 1 as amended satisfies the requirements of 35 C.F.R. § 112, first paragraph. Applicants' invention is directed to method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. It will be appreciated that any composition, provided that it includes a purified antibody specific against C5, will, if used in accordance with the claimed method, fall within the scope of Applicants' invention in accordance with the teachings of Applicants' specification as understood by those of skill. It continues to be Applicants' intent that "comprising" as it appears in the claims is to be given in each instance its traditional open meaning, and that compositions comprising a purified antibody specific against C5 and additional active and inactive ingredients properly fall within the contemplated scope of Applicants' invention. Accordingly, it is believed that withdrawal of the Examiner's rejection is proper, and the same is respectfully requested.

With respect to the Examiner's comments regarding the 5G1.1 antibody of claim 18, Applicants respectfully direct the Examiner's attention to page 60, lines 4-10 of the specification, which states that the 5G1.1 hybridoma was deposited with the American Type Tissue Collection on April 27, 1994 in accordance with the conditions of the Budapest Treaty. Applicants hereby state that, in accordance with the Budapest Treaty, all restrictions imposed by the depositor on the availability to the public of the deposited 5G1.1. hybridoma will be irrevocably removed upon the granting of a patent. Accordingly, Applicants submit that claim 18 satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph, and that the Examiner's rejection may properly be withdrawn.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-14 and 17-18 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for the recitation of the phrase "composition comprising at least one purified antibody specific against C5" because "the metes and bounds of this limitation [are] not clear" (04/05/01 Office Action, paragraph 9A).

The Examiner's interpretation of this traditional open language is not understood, but in a sincere attempt to advance prosecution, claim 1 has been amended to delete recitation of "at least one" which appears to have confused the Examiner, and to recite "composition comprising a purified antibody specific against C5." No new matter has been added by way of this amendment, for which support is found throughout the specification, *e.g., inter alia,* at page 29, lines 14-21, and Examples 1-8, pages 37-60.

Applicants submit that claim 1 as amended satisfies the requirements of 35 C.F.R. § 112, second paragraph. Applicants' invention is directed to method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. It will be appreciated that any composition, provided that it includes a purified antibody specific against C5, will, if used in accordance with the claimed method, fall within the scope of Applicants' invention in accordance with the teachings of Applicants' specification as understood by those of skill. It continues to be Applicants' intent that "comprising" as it appears in the claims is to be given in each instance its traditional open meaning, and that compositions comprising a purified antibody specific against C5 and additional active and inactive ingredients properly fall within the contemplated scope of Applicants' invention. Accordingly, it is believed that withdrawal of the Examiner's rejection is proper, and the same is respectfully requested.

Claims 2-14 and 17-18 also stand rejected under 35 U.S.C. § 112, second paragraph, as the recitation of "C5 blocker" lacks proper antecedent basis (04/05/01 Office Action, paragraph 9B). The Examiner is thanked for pointing out this obvious error in the claim language, the result of inadvertently failing to correctly recite "composition," which is the grammatical antecedent of the dependent claims. Accordingly, Applicants have amended each dependent claim to recite "composition," and respectfully request that the rejection be reconsidered and withdrawn.

Claim 18 also stands rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "5G1.1" because 5G1.1 is a laboratory designation (04/05/01 Office Action, paragraph 9C).

This ground of rejection is respectfully traversed.

Applicants have described the preparation of the hybridoma 5G1.1 (Specification, Example 8, pages 56-60) and have further deposited the hybridoma 5G1.1 with the American Type Culture Collection (Specification, page 60). One skilled in the art would understand that the 5G1.1 antibodies are derived from the deposited 5G1.1 hybridoma using standard laboratory techniques. Thus, Applicants respectfully submit that the recitation of "5G1.1" in the claim is not indefinite and that this ground of rejection may be properly withdrawn.

Finally, Applicants acknowledge with thanks the Examiner's suggestion to specifically point out support for any amendments made to the disclosure. However, it is believed that no amendments have been made to the disclosure in prosecution of the application, other than correction of typographical errors and to update priority application status information.

III. Rejection Under 35 U.S.C. 103(a)

Claims 1-14 and 17-18 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sindelar *et al.* (U.S. Patent No. 5,173,499) in view of Auda *et al.* (Pheumatol. Int. 10:185-18 (1990)), Wurzner *et al.* (Complement Inflamm. 8:328-40 (1991)) and Montz *et al.* (Cell. Immunol. 127:337-51 (1990)) (04/06/01 Office Action, paragraph 11).

This ground of rejection is respectfully traversed.

The Examiner states that Sindelar *et al.* teaches methods for treating established joint inflammation comprising the administration of an effective amount of a C5 blocker. Auda *et al.* is cited to teach the measurement of complement activation products in patients suffering chronic

rheumatic diseases to predict patient clinical status. Auda *et al.* is also cited to teach monitoring C5b-9 levels in patients to provide a more sensitive indicator of patient status. Wurzner *et al.* is cited to teach the inhibition of terminal C components by monoclonal antibodies specific for C5. Montz *et al.* and Wurzner *et al.* are further cited to teach C5 inhibitors, which do not affect the early C components. The Examiner asserts that one of ordinary skill in the art would have been motivated to modify the teachings of Sindelar *et al.* with the teachings of Auda *et al.*, Montz *et al.* and Wurzner *et al.* to use C5 inhibitory antibodies to inhibit inflammatory joint disease. The Examiner contends that the motivation to combine the references is in the use of analogous compounds to those taught in Sindelar *et al.* for the inhibition of C5 activity with a reasonable expectation of success, although the Examiner does not appear to contend that the asserted motivation may be found within the cited references themselves. (*See* 03/31/96 Office Action).

The Sindelar *et al.* patent is directed to chemically synthesized non-protein organic compounds for the inhibition and/or suppression of immune activity, which do not fall within the scope of the Applicants' claims for the use of a purified antibody specific against C5. Moreover, as the Examiner's implicitly acknowledged in withdrawing the prior rejection under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 130(a) as obvious over the Sindelar *et al.* reference, Sindelar *et al.* does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody specific against C5.

In an attempt to cure the deficiencies of Sindelar *et al.*, the Examiner cites Wurzner *et al.* and Montz *et al.* While Wurzner *et al.* discuss the production of two monoclonal antibodies

against C5, the specific use of these monoclonal antibodies to treat joint inflammation is not taught or suggested. It is not disputed that monoclonal antibodies against C5 existed prior to Applicants' invention; however, Applicants submit that the effective use of a composition comprising a purified antibody specific against C5 in a method for the treatment of established joint inflammation was not known in, much less suggested by, the prior art. The Montz *et al.* reference discusses experiments to determine the potential role of endogenously synthesized C5 and subsequently generated C5a in an autologous T cell stimulation. Therefore, the Montz *et al.* reference is directed to analyzing the inhibitory effect of anti-C5a against autologous T cell proliferative responses. Montz *et al.* does not teach or suggest the use of compositions comprising a purified antibody specific against C5 for the treatment of established joint inflammation. Therefore, neither Wurnzer nor Montz teaches or suggests the use of anti-C5 antibodies to treat established joint inflammation, and thus neither supplies the deficiencies of Sindelar *et al.*, alone or in combination.

Finally, Auda *et al.* does nothing to remedy the deficiencies of Sindelar *et al.*, Wurzner *et al.*, and Montz *et al.* Auda *et al.* merely describes measuring complement activation products in patients. Auda *et al.* does not teach or suggest the claimed method of treating established joint inflammation by administering to a patient a composition comprising a purified antibody specific against C5. Further, Auda *et al.* does not provide any motivation to combine the references cited by the Examiner.

It is not sufficient that the prior art *can be* modified to produce the claimed invention. Rather, the modification is non-obvious unless the prior art suggests the desirability thereof. *In*

re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989). Further, the invention as a whole must be considered when determining obviousness, and it is improper to consider only the obviousness of any substitution or modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Indeed, modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "unless the prior art suggests the desirability of the modification." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Applicants respectfully submit that the asserted motivation to combine the references is lacking.

Accordingly, Applicants respectfully request withdrawal of the instant rejection.

Claims 1-14 and 17-18 also stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sindelar *et al.*, in view of Auda *et al.*, Wurzner *et al.* and Montz *et al.* in further view of Rollins *et al.* (U.S. Patent No. 5,853,722) (04/05/01 Office Action, paragraph 11).

Applicants respectfully traverse this ground of rejection.

The Examiner asserts that Rollins *et al.* is added to allegedly provide further teachings and evidence that C5-specific antibodies had the property of inhibiting complement inflammatory conditions in humans at the time the invention was made.

The Sindelar *et al.*, Auda *et al.*, Wurzner *et al.*, and Montz *et al.* references are discussed above. Rollins does not remedy the deficiencies of the combination of Sindelar *et al.* in view of Auda *et al.*, Wurzner *et al.*, and Montz *et al.* Rollins teaches the use of anti-C5 antibodies to block the generation of activated complement components C5a and C5b following extracorporeal circulation during cardiopulmonary bypass. Indeed, Rollins specifically teaches

that "[m]ore generally, the invention relates to the use of anti-C5 antibodies in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient" wherein the "anti-C5 antibody is used to reduce at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion resulting from the circulation of the patient's blood through such a conduit" (Rollins, columns 10-11). While Rollins suggests that the anti-C5 antibody can be used to reduce complement activation caused by taking blood and circulating it through a conduit, Rollins does not teach or suggest the Applicants' claimed method of treating established joint inflammation by administering to a patient a composition comprising purified antibody specific against C5.

Thus, Rollins does not supply the deficiencies of Sindelar *et al.*, Auda *et al.*, Wurzner *et al.*, and Montz *et al.* Further, the motivation to combine the references is lacking, because none of the prior art references suggests the desirability of modification of the references. Accordingly, withdrawal of the rejection is respectfully requested.

Finally, claims 1-14 and 17-18 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sindelar *et al.* in view of Auda *et al.*, Wurzner *et al.* and Montz *et al.* in further view of Rollins *et al.* and Wang *et al.* (U.S. Patent No. 6,074,642) (04/05/01 Office Action, paragraph 11). Applicants respectfully traverse the rejection.

The Examiner cites Wang as disclosing the anti-C5 antibody 5G1.1, which allegedly "has the properties encompassed by the claimed invention, including its use in treating an inflammatory/autoimmune condition." The Examiner further opines that given these asserted

properties of the 5G1.1 antibody, one skilled in the art "would have been motivated to substitute the anti-C5 5G1.1 antibody in the instant methods of inhibiting another inflammatory or autoimmune condition" (04/05/01 Office Action, paragraph 11).

It is submitted that Wang *et al.* actually teaches a monoclonal antibody specific for complement component C5 for use in treating glomerulonephritis, an immune complex disease of the kidneys. Wang does not teach or suggest a method of treating established joint inflammation by administering to a patient a composition comprising a purified antibody specific against C5.

Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Yi Wang pursuant to 37 C.F.R. § 1.132 submitted 12 September 1996. While anti-C5 monoclonal antibodies were effective in the treatment of glomerulonephritis, Dr. Wang declares that it was not known that the method claimed in the instant application would be successful in treating established joint inflammation. Indeed, several references had been published which taught away from the present invention, i.e., that animals carrying a genetic defect, which caused them to have no C5, still developed established joint inflammation (Wang Declaration, paragraph 4, and references cited therein).

Thus, Applicants submit that the required motivation to combine the Sindelar, Auda, Wurzner, Montz, Rollins and Wang references is completely lacking. Modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "unless the prior art suggests the desirability of the modification." *In re Fritch*, 23

U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Not one reference, either alone or in combination with the other references, discloses or suggests the desirability of the claimed invention.

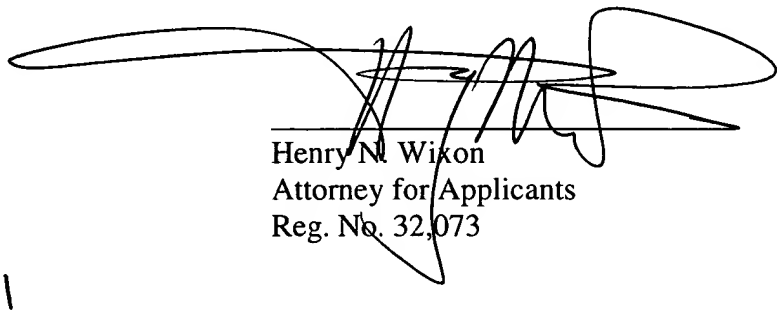
Accordingly, withdrawal of this ground of rejection is believed proper, and is respectfully requested.

IV. Conclusion

In view of the foregoing remarks and amendments, Applicants believe that the application is now in condition for immediate allowance. If the Examiner believes that an interview would assist in advancing the prosecution of the application, he is invited to call the undersigned at the number set forth below.

If there are any fees due in connection with the filing of this response and not otherwise authorized, please charge the fees to Deposit Account No. 08-0219. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is hereby petitioned and the fee should also be charged to Deposit Account No. 08-0219.

Respectfully submitted,



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APPENDIX B

AMENDED CLAIMS 1, 2, 4, 6, 8-11 AND 14 – MARKED-UP VERSION

1. (Four Times Amended) A method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising [at least one]a purified antibody specific against C5.

2. (Amended) The method of Claim 1 wherein the [C5 blocker]composition is administered in an amount effective to inhibit the cell-lysing capability of complement present in a blood-derived fluid of the patient.

4. (Amended) The method of Claim 1 wherein the [C5 blocker]composition is administered in an amount effective to reduce the level of soluble C5b-9 present in a blood-derived fluid of the patient after activation of complement in that fluid.

6. (Amended) The method of Claim 1 wherein the [C5 blocker]composition is administered in an amount effective to reduce the level of C5a present in a blood-derived fluid of the patient after activation of complement in that fluid.

8. (Amended) The method of Claim 1 wherein the [C5 blocker]composition is administered in an amount effective to reduce the cell-lysing ability of complement present in the synovial fluid of an inflamed joint of the patient by at least 10%.

9. (Amended) The method of Claim1 wherein the [C5 blocker]composition is administered in an amount effective to reduce the level of soluble C5b-9 present in the synovial fluid of an inflamed joint of the patient by at least 10%.

10. (Amended) The method of Claim 1 wherein the [C5 blocker]composition is administered in an amount effective to reduce the level of C5a present in the synovial fluid of an inflamed joint of the patient by at least 10%.

11. (Amended) The method of Claim 1 comprising the further step, after the administration of the [C5 blocker]composition, of determining the C5a level and/or the C5b level in the synovial fluid of an inflamed joint of the patient so as to monitor the course of the patient's response to the administration of the [C5 blocker]composition.

14. (Amended) The method of Claim 1 wherein the [C5 blocker]composition does not interfere with the cleavage of complement component C3 in the patient's serum into C3a and C3b.

APPENDIX D

AMENDMENT TO SPECIFICATION - PAGE 1, AFTER TITLE – MARKED-UP COPY

Related Applications

This application is a continuation application of [copending]application Serial No. 08/311,489, filed on September 23, 1994, abandoned.